

# TARGETING THE UROGENITAL HEALTH OF POSTMENOPAUSAL WOMEN: A SPOTLIGHT ON VAGINAL ATROPHY

**INTRODUCTION** - by Susan Wysocki, WHNP-BC, FAANP

Estrogen deprivation associated with menopause is the major cause of urogenital atrophy in menopausal women. Atrophic changes of the vagina, vulva, and urinary tract have a large impact on quality of life (QoL), with symptoms being progressive in nature and worsening with time. Common symptoms of urogenital atrophy include vaginal dryness, irritation, and itching; pain during sexual intercourse; and recurrent urinary tract infection (UTI).

Observational studies have confirmed the high prevalence of urogenital atrophy, reporting its occurrence in 27%-59% of peri- and postmenopausal women.<sup>1-4</sup> Vaginal dryness is similarly frequent, occurring in up to one-half of postmenopausal women; its prevalence increases exponentially with amount of time since menopause.<sup>2,3</sup> Approximately one-third of postmenopausal women experience pain during sexual intercourse, and a similar fraction report difficulty with vaginal lubrication,<sup>2,5,6</sup> causing many women to avoid or lose interest in sex.<sup>2,7</sup> In addition, 7% of postmenopausal women aged 50-75 develop UTIs.<sup>8</sup> Although urogenital atrophy is highly prevalent, many women are reluctant to openly discuss their discomfort, especially their symptoms related to sexual function, with a clinician. Fewer than 25% of women with urogenital atrophy receive appropriate care for it.<sup>9</sup>

## LEARNING OBJECTIVES

At the end of this educational program, participants will be able to:

- Understand the role of NPs and PAs in evaluating, counseling, and treating patients with urogenital atrophy.
- Consider the role of estrogen deficiency in the pathogenesis and pathophysiology of urogenital atrophy.
- Review the typical clinical presentation of women with vaginal atrophy.
- Discuss the role of patient counseling in the management of patients with postmenopausal urogenital symptoms.
- Review techniques for discussing urogenital health in your female patients.
- Consider the efficacy of hormonal and nonhormonal therapies for managing the symptoms of urogenital atrophy.



This program has been reviewed and is approved for a maximum of one hour of AAPA Category I CME credit by the Physician Assistant Review Panel. Approval is valid for one year from the issue date of October 2009. Participants may submit the self-assessment at any time during that period.

This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

Successful completion of the self assessment is required to earn Category I CME Credit. Successful completion is defined as a cumulative score of at least 70% correct.

To obtain CME credit please go to [www.cmeuniversity.com/va](http://www.cmeuniversity.com/va) for a brief outcomes evaluation. You will then be redirected to AAPA's website to take the post-test and receive your AAPA Category I CME credit. You will need your AAPA ID and password in order to log in and complete the post-test.

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Healthcare practitioners (HCPs) need to engage menopausal patients in a comfortable conversation regarding sexual and urogenital symptoms. By using open-ended questions and directed follow-up queries, HCPs can better understand menopausal women's complaints. Because symptoms associated with urogenital atrophy do not resolve without treatment, prompt diagnosis and treatment are critical. Several safe and effective treatment options exist, including nonhormonal remedies, hormonal therapies, and lifestyle modifications. Timely and careful assessment of these women, as well as customizing treatment based on their individual needs, may facilitate successful outcome and enhance QoL.

In this supplement to *Women's Health Care: A Practical Journal for Nurse Practitioners* and *The Monitor*, experts in the field of women's health provide important reviews using a case-based approach to recognize, diagnose, and treat urogenital atrophy. In the first article, Linda Burdette, MPAS, PA-C, discusses the prevalence, diagnosis, and treatment of vaginal and urinary symptoms associated with urogenital atrophy. In the second article, Suzanne Reiter, WHNP-BC, MM, MSN, SANE-A, FAANP, reviews the incidence, pathophysiology, diagnosis, and treatment of sexual dysfunction and vaginal atrophy in menopausal women, with a focus on establishing effective communication toward a successful outcome. We hope that the information contained in this supplement will be helpful and assist you in your efforts to diagnose and treat urogenital atrophy in your patients.

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# MANAGING THE VAGINAL AND URINARY SYMPTOMS OF POSTMENOPAUSAL UROGENITAL ATROPHY: A CASE-BASED APPROACH

by Linda Burdette, MPAS, PA-C

## CASE PRESENTATION: PATIENT HISTORY

A 65-year-old female college professor presents to her clinician complaining of increasing vulvar and vaginal irritation, including external vulvar and vaginal dryness, itching, and burning. These symptoms started about 3 years ago and have caused her considerable discomfort and embarrassment, particularly when she is in the classroom. Two months ago, she started using an over-the-counter vaginal anti-itch cream, but her symptoms persist. Dyspareunia is not an issue because she has no sexual partner. The patient also has a notable history of recurrent urinary tract infections (UTIs), which began about the same time as her vaginal symptoms. She has received many antibiotic treatments, as well as periodic oral antifungal therapy with fluconazole. In the past 6 months, she has followed a prophylactic antibiotic regimen of nitrofurantoin 100 mg daily and has had excellent control of her UTIs. Both her vaginal symptoms and UTIs began after she discontinued oral estrogen therapy, which she had used after undergoing a hysterectomy and bilateral oophorectomy in her late 40s.

## PREVALENCE AND IMPACT OF UROGENITAL ATROPHY

Urogenital atrophy is a highly prevalent but largely underrecognized and undertreated consequence of menopause and estrogen deficiency.<sup>1</sup> Symptoms of urogenital atrophy include vaginal dryness, itching, and irritation; pain during sex; and recurrent UTIs. Unlike other symptoms associated with menopause, such as hot flashes, those of urogenital atrophy often worsen with advancing age. Because life expectancy in women is nearly 80 years, women may experience symptoms of urogenital atrophy for more than one-third of their life; however, fewer than 25% of women who experience these symptoms receive treatment for them.<sup>2,3</sup>

Urinary symptoms associated with urogenital atrophy are common—20% of noninstitutionalized elderly women experience bacteriuria<sup>4</sup> and 12%–17% of postmenopausal women experience UTIs.<sup>4,5</sup> Vulvovaginal or urinary atrophic symptoms in postmenopausal women can cause significant reductions in quality of life, avoidance of sexual intercourse, and emotional distress.<sup>6</sup> In a survey of 2290 postmenopausal women, 59% of those not currently using estrogen therapy (ET) reported that they currently experienced symptoms of urogenital atrophy.<sup>7</sup> Among this group, 92% found the symptoms at least somewhat bothersome and nearly half found the symptoms moderately or very bothersome.<sup>7</sup>

## PHYSICAL EXAMINATION

A physical examination shows that the patient has thinning vulvar tissues, a small introitus, and hypochromic changes to the vulvar and vaginal tissues. A pediatric speculum is used because she has a substantial loss of elasticity of the introitus.

## PATHOPHYSIOLOGY OF UROGENITAL ATROPHY

Estrogen stimulation is required for female urogenital tissues to maintain normal structure and function.<sup>6</sup> In fact, receptors for estrogen are found not only in the vagina and vulva, but also in the neck of the bladder and the urethra.<sup>8,9</sup> The declining estrogen levels that characterize menopause lead to numerous cytologic and structural changes in the vagina, vulva, and lower urinary tract.<sup>10</sup>

**Vulvovaginal Changes**—Vaginal cytologic changes associated with estrogen deficiency include a significant decrease in the proportion of intermediate and superficial cells and an increase in the proportion of parabasal cells.<sup>10,11</sup> The vaginal maturation index, a measure of the percentage of parabasal, intermediate, and superficial squamous cells noted on a cytologic smear, has been used to determine the degree of vaginal atrophy in many clinical trials. In addition, losses in collagen content and adipose tissue in the vagina are commonly seen with menopause, resulting in a thinning of the epithelial surface.<sup>12</sup> Estrogen deficiency also leads to a shortening and narrowing of the vagina and the thinning of the vaginal walls, which become less elastic and increasingly pale.<sup>10</sup> Together, these changes can result in vaginal dryness, itching, burning and dyspareunia. Estrogen loss also interferes with several physiologic aspects of the female sexual response, causing reduced smooth muscle relaxation, decreased vaginal blood flow, and decreased and delayed vaginal secretions.<sup>6</sup>

**Urinary Tract Changes**—Like other urogenital tissues, the mucosa of the urethra, the bladder, and the connective tissue surrounding the urethra are sensitive to estrogen. After menopause, the urethral mucosa atrophies and the collagen content in the connective tissue surrounding the urethra decreases.<sup>3</sup> Estrogen deficiency in the urinary tract also results in changes in vaginal pH.<sup>6</sup> In premenopausal women, estrogen maintains an acidic vaginal pH that prevents the growth of pathogenic bacteria. As estrogen declines, vaginal pH rises, increasing the likelihood of vaginal colonization by pathogens.<sup>6,10</sup> Blood flow in the urethra is also reduced.<sup>3</sup> These changes predispose women to vaginal infections and recurrent UTIs caused by a variety of pathogens.<sup>3</sup>

## DIAGNOSIS

This patient has significant urogenital atrophy, the cause of both her vaginal and vulvar symptoms. Urogenital atrophy also likely contributes to her vulnerability to UTIs.

## PATIENT EVALUATION

**Health History**—Most cases of urogenital atrophy result from estrogen deficiency related to menopause.<sup>10</sup> If urogenital atrophy occurs before the usual age of menopause, other conditions that reduce estrogen levels should be considered. These conditions include premature ovarian failure, hyperprolactinemia, lactation, use of progestin-only contraceptives, use of certain endocrine therapies (eg, aromatase inhibitors), pharmacologically induced menopause related to the use of gonadotropin-releasing hormone agonists, use of chemotherapy, and exposure to radiation therapy.<sup>10</sup> Therefore, a thorough health history is critical in women reporting vaginal atrophy.<sup>10</sup>

**Physical Examination**—The pelvic examination of postmenopausal women includes screening for vaginal atrophy, even in those not complaining of atrophic symptoms. Signs of vaginal atrophy observed during the physical examination vary with the duration of estrogen deficiency and the degree of vaginal atrophy.<sup>10</sup> In women with vaginal atrophy, key findings include a thin and dry vaginal epithelium; pale, thin, and dry vulvar tissues; tenderness to palpation; reduced vaginal elasticity; vaginal narrowing; and an increased susceptibility to trauma and irritation. Wet-mount microscopy usually shows immature vaginal epithelial cells with large nuclei (parabasal cells), minimal or absent lactobacilli, and more than 1 white blood cell per epithelial cell.<sup>10</sup> Of note, vaginal pH is typically greater than 5.0.

## TREATMENT OF UROGENITAL ATROPHY

Key goals for treating women with signs of urogenital atrophy are to alleviate symptoms and reduce or reverse the atrophic changes. Various nonhormonal and hormonal treatment options have been used to accomplish these goals.

**Nonhormonal Treatment Options**—Certain lifestyle modifications may improve the symptoms of vaginal atrophy.<sup>13,14</sup> For example, smoking cessation, regular coital activity, avoidance of heavily scented and anti-itch products, and wearing loose-fitting cotton underwear may be useful. Women with recurrent UTIs also may benefit from the use of prophylactic antibiotics or regular consumption of cranberry juice (eg, 200–750 mL daily).<sup>15</sup>

Water-soluble vaginal lubricants are useful in temporarily relieving vaginal dryness during intercourse. Oil from vitamin E capsules has also been reported to be beneficial.<sup>16</sup> Vaginal moisturizers may provide more long-term relief of vaginal dryness. These formulations have been shown to reduce itching, irritation, and dyspareunia and may have a favorable effect on the maturity of the vaginal epithelium.<sup>17–19</sup> Vaginal moisturizers are particularly useful in women in whom ET may be inappropriate, such as those with a history of hormone-dependent cancers.

**Estrogen Therapy**—Because estrogen deficiency is the underlying cause of urogenital atrophy, ET is a logical treatment strategy for women complaining of vulvovaginal and urinary symptoms. Both systemic and local ET produce significant improvements in symptoms due to urogenital atrophy.<sup>10</sup>

**Systemic Estrogen Therapy.** Systemic ET delivered by the oral, transdermal,

or systemic intravaginal route has significant benefits in treating vaginal atrophy, relieving vasomotor symptoms, and preventing osteoporosis.<sup>10</sup> However, systemic ET requires concomitant therapy with a progestin in women with a uterus and may be associated with adverse effects such as endometrial bleeding, breast tenderness, a small increase in the risk of venous thromboembolism and stroke, and, when used with a progestin, breast cancer.<sup>20,21</sup> Therefore, systemic ET may be contraindicated in or unacceptable to some women.<sup>10</sup>

**Local Vaginal Estrogen Therapy.** Local low-dose ET with a vaginal cream, ring, or tablet (Table) may be more appropriate for women who do not require the systemic effects of other estrogen formulations or who wish to avoid using systemic ET. These vaginal formulations provide sufficient estrogen to reverse many atrophic changes, with limited systemic absorption.<sup>10</sup> According to the 2007 position statement by The North American Menopause Society (NAMS) on the treatment of vaginal atrophy, local vaginal estrogen is well tolerated and has been shown to reduce atrophic symptoms and increase vaginal pH.<sup>10</sup> In addition, a recent Cochrane review on the impact of estrogens in preventing recurrent UTIs concluded that vaginal estrogens reduced the number of UTIs in women with recurrent UTIs, although this conclusion was based on only two placebo-controlled studies of vaginal estrogen.<sup>22</sup> Advantages of local ET include its limited systemic exposure, reduced risk of adverse effects compared with systemic formulations, and the ability to be administered without concomitant progestin therapy.<sup>23</sup>

**Cream Formulations.** Clinical trials have demonstrated that conjugated estrogen (CE) vaginal cream in doses of 0.5-2.0 g (delivering 0.3-1.25 mg CE) and estradiol vaginal cream are effective in relieving vaginal symptoms.<sup>17,24-28</sup> Moreover, a study of estriol vaginal cream in women with recurrent UTIs also showed that treatment reduced the incidence of recurrent UTIs.<sup>29</sup> Estrogen creams, when used in low doses twice a week, may be the least expensive means of delivering vaginal estrogen.

However, vaginal estrogen cream can be underdosed or overdosed because the various formulations are not available in prepackaged doses. The creams also are associated with poor rates of patient adherence, possibly because of their messiness and relative inconvenience.<sup>30,31</sup> Higher rates of systemic absorption have been reported with the estrogen creams than with the estrogen tablet or the non-systemic-dose ring,<sup>31,32</sup> particularly with the older regimens for the creams, which entail more cream than is typical with the newer regimens.

**Ring Formulation.** A vaginal estrogen ring that releases estradiol at a dosage of 7.5 mcg every 24 hours for 90 days has shown superior efficacy to placebo and similar efficacy to vaginal creams and the vaginal tablet in relieving symptoms of vaginal atrophy, restoring vaginal pH, and improving vaginal cytologic findings.<sup>26,27,33,34</sup> The non-systemic-dose vaginal estrogen ring also has been shown to prolong the time to UTI recurrence and decrease the number of UTI recurrences in a randomized, open-label study of postmenopausal women with recurrent symptomatic UTIs.<sup>35</sup>

Although patient acceptability of the ring is greater than that reported for the vaginal cream, some women with limited manual dexterity or severely reduced vaginal capacity may have difficulty inserting it.<sup>13</sup> Dislodgement of the ring in women with pelvic organ prolapse may also occur.

**Tablet Formulation.** The vaginal estrogen tablet is administered by applicator and gradually dissolves, slowly releasing estrogen to the vaginal wall. Studies have shown that the estradiol-containing vaginal tablet effectively relieves vaginal symptoms, decreases vaginal pH, and increases maturation of the vaginal and urethral epithelium.<sup>36-38</sup> A recent study demonstrated that ultra-low-dose vaginal estradiol (10 mcg), compared with placebo, increased vaginal maturation, improved vaginal health, restored vaginal pH, and reduced vaginal symptoms.<sup>38</sup> Compared with vaginal estrogen creams, the vaginal tablet provides a more consistent dose of estrogen and reduces the potential for leakage.<sup>25,30,39</sup> Women using the vaginal tablet, compared with those using a vaginal cream, are also more likely to adhere to their treatment regimen and continue treatment for longer periods of time.<sup>30</sup> The potential disadvantage of the vaginal tablet is that, because of the twice-a-week dosing schedule, women may forget to insert a tablet now and then.

**Emerging Hormonal Treatment Options—**Two other types of hormonal therapies are under investigation as alternatives to ET in patients with urogenital atrophy. These therapies include selective estrogen receptor modulators (SERMs) and dehydroepiandrosterone (DHEA). Neither option is FDA-approved for use in managing vaginal atrophy.

**Selective Estrogen Receptor Modulators.** SERMs may be a useful therapeutic alternative to local ET in some women with urogenital atrophy. Evidence suggests

that two SERMs in clinical development, lasofoxifene and ospemifene, may improve vaginal maturation, relieve vaginal dryness, and reduce pain during sex.<sup>40,41</sup>

**Dehydroepiandrosterone.** Recent studies have evaluated the impact of intravaginal administration of DHEA in women experiencing atrophic symptoms.<sup>42,43</sup> Treatment with intravaginal DHEA has been shown to increase vaginal maturation, decrease vaginal pH, and improve vaginal symptoms without stimulating the endometrium.<sup>42,43</sup>

#### PATIENT MANAGEMENT

Because local estrogen formulations are similar in efficacy,<sup>32</sup> women should use the preparation they prefer,<sup>3</sup> keeping in mind the relative convenience of each formulation. Clinical treatment guidelines recommend that vaginal estrogen be titrated to the lowest effective dose and frequency necessary to provide the desired effect.<sup>10</sup>

Local estrogen formulations are well tolerated. However, some clinicians may be concerned about the risk for endometrial hyperplasia in women with an intact uterus. Because most studies have demonstrated no endometrial hyperplasia with low-dose vaginal estrogen formulations, NAMS suggests that concomitant treatment with a progestin is not indicated and that routine endometrial surveillance is not recommended in asymptomatic women at low risk for adverse endometrial effects.<sup>10</sup>

#### CASE PREVENTION: TREATMENT AND FOLLOW-UP

The patient agrees to try local low-dose ET delivered by a vaginal cream. After demonstrating that she understood its application by inserting a sample during her office visit, she is instructed to insert one dose into the vagina approximately every 4 days (ie, twice a week). If the applicator is too uncomfortable, she can apply the same amount of cream with a finger instead. Therapy with nitrofurantoin 100 mg daily is continued. She is advised to stop using over-the-counter anti-itch products because they are a common cause of contact or irritant dermatitis. Finally, she is instructed to avoid harsh soaps and aggressive scrubbing and to ensure adequate fluid intake.

A follow-up visit is scheduled in 3 months. If, in 3 months, she shows improvement in her signs and symptoms, the patient will be advised to try discontinuing nitrofurantoin. She is advised that she will likely require long-term vaginal ET to minimize her need for antibiotic therapy and prevent future vulvovaginal itching, vulvovaginal irritation, and frequent UTIs.

#### CONCLUSION

Urogenital atrophy is a common problem among postmenopausal women that significantly affects vulvovaginal health, sexual functioning, urinary health, and quality of life. Because estrogen deficiency related to the menopause transition is the major cause of urogenital atrophy, ET is a logical choice of treatment for women who suffer from its symptoms. Although both systemic and local ETs are effective in relieving vaginal dryness, vaginal itching, and dyspareunia; preventing recurrent UTIs; and reversing some of the signs of urogenital atrophy, low-dose local ET has several important advantages, including a lack of systemic effects. Local vaginal estrogen products are available in cream, ring, and tablet formulations, all of which are effective and well tolerated, although adherence rates to the ring and tablet regimens are slightly higher. The choice and duration of therapy should be individualized, depending on the needs and preferences of each woman.

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#### TABLE: VAGINAL ESTROGEN PRODUCTS APPROVED FOR USE IN THE UNITED STATES

Formulation	Product Name	Dosing
Vaginal Cream	Estrace*	Initial: 2.0-4.0 g/d for 1-2 weeks
		Maintenance: 1.0 g/d
Conjugated estrogens	Premarin*	Cyclic 0.5-2.0 g/d
		Alternative: 0.5 g twice weekly
Vaginal ring	Estring*	Device containing 2 mg releases 7.5 mcg/day for 90 days
		Estradiol acetate
Vaginal tablet	Vagifem*	Initial: 1 tablet/d for 2 weeks
		Maintenance: 1 tablet twice weekly (tablet containing 25.8 mcg of estradiol hemihydrate equivalent to 25 mcg/day of estradiol)

Adapted from The North American Menopause Society. The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. *Menopause*, 2007;14 (3 pt 1):355-369. Reprinted with permission.

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# SEXUAL DYSFUNCTION AND VAGINAL ATROPHY IN MENOPAUSAL WOMEN: AN APPROACH TO EFFECTIVE COMMUNICATION AND MANAGEMENT

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## CASE PRESENTATION: PATIENT HISTORY

A 52-year-old woman who has undergone natural menopause reports dyspareunia and vaginal itching, burning, and dryness, and complains that her symptoms have become more severe since her last checkup a year ago. The patient is reluctant to elaborately discuss her sexual problems; however, with further questioning, she reports that intercourse has been so painful lately that she has lost her desire for sexual activity.

## INTRODUCTION

Menopause is characterized by a decline in ovarian function and a decrease in systemic estrogen levels.<sup>1</sup> Menopause can be natural, surgically induced, chemically induced, or due to premature ovarian failure.<sup>2</sup> Estrogen plays a critical role in maintaining the structure and function of the female urogenital system, including the vulva, vagina, bladder, urethra, pelvic floor, and endopelvic fascia.<sup>3,4</sup> Vaginal atrophy is one of the most common manifestations of estrogen deprivation, when circulating levels of estrogen are dramatically reduced from premenopausal levels ( $\geq 120$  pg/mL) to postmenopausal levels ( $\sim 10$ -20 pg/mL).<sup>2</sup>

Vaginal and vulvar irritation, dryness, itching, and burning; leukorrhea; and dyspareunia are the commonly reported symptoms of urogenital atrophy, which result in tremendous discomfort and decreased libido and quality of life.<sup>5,6</sup> Urinary symptoms associated with urogenital atrophy include increased urgency and frequency, stress incontinence, and recurrent urinary tract infections (UTIs).<sup>2,7-9</sup>

Fifty percent of postmenopausal women aged 50-60 years and approximately 72% of those aged  $\geq 70$  years experience vaginal dryness.<sup>10,11</sup> Dyspareunia can affect up to 40% of women older than 50.<sup>12</sup> Despite such a high prevalence of vaginal dryness and dyspareunia, only a small fraction of women with these problems seek clinical attention. Women are particularly hesitant to discuss sexual problems with their clinician.<sup>13</sup> Reluctance to discuss sexual health can be attributed to embarrassment, cultural beliefs, anxiety regarding the clinician's response, and lack of sufficient knowledge of available treatment options. Reluctance on the clinician's part to discuss sexual dysfunction may be due to a lack of expertise in sexual assessment, lack of knowledge about treatment options, or time constraints.<sup>14</sup>

## NEED FOR ESTABLISHING HEALTH HISTORY AND SEXUAL HISTORY

Engaging a menopausal patient in a conversation helps document predisposing factors for sexual dysfunction. The clinician should ask whether the patient has experienced vaginal dryness, vaginal itching/irritation, or postcoital bleeding, spotting, or soreness. A health history will help identify other hypoestrogenic conditions such as premature ovarian failure; hyperprolactinemia; hypothalamic amenorrhea; or a history of cancer treatment such as surgery, radiation, and/or chemotherapy.

The clinician also needs to elicit the patient's sexual history in terms of current sexual activity, partners, and treatments or interventions used for sexual dysfunction. Taking a sexual history will enable the examiner to identify problems related to affect, desire, excitement, arousal, orgasm, and/or dyspareunia.<sup>15</sup> Vaginal dryness leads to painful intercourse and decrease in sexual desire.<sup>16,17</sup>

## INITIATING A CONVERSATION

Given the reluctance for both patients and practitioners to discuss sexual health issues, it is important to engage the patient in a more detailed discussion about their symptoms. Asking directly about the frequency of painful intercourse, increased urinary frequency, and recurrent UTIs seldom leads to a correct diagnosis. To make the patient feel comfortable, the clinician can start the conversation with any of these approaches:

- "Many women come to our office because of changes in the vaginal area, such as dryness, itching, and pain with sex. Other women tell us that they urinate more often, have burning while urinating, or leak urine. Are you experiencing anything like this?"
- "Have you experienced changes in your vaginal area, such as dryness, burning, or itching?"
- "Tell me about your sexual activity—have you ever experienced any pain with intercourse or afterward?"
- "Have you tried any lubricants?"

## PHYSICAL EXAMINATION AND DIAGNOSIS

A pelvic examination confirms that the patient has an intact uterus and ovaries but demonstrates a loss of labial and vulvar fullness, pallor of the urethral and vaginal epithelium, a marked decrease in vaginal rugae and moisture, and a vaginal pH of 6.5. Clinical examination also shows the presence of minor petechiae, and bleeding is observed with insertion of the speculum.

**Clinical Examination**—Upon examination, the patient's external genitalia demonstrate diminished elasticity, turgor, sparsity of pubic hair, labial dryness, vulvar dermatoses, and fusion of the labia minora (Table).<sup>2,18</sup> Normal physiologic levels of estrogen are associated with thickened and mature vaginal mucosa. Reductions in estrogen levels lead to thin, shiny, and pale, friable mucosa, with loss of rugae, characterized by granulation, fissures, ecchymoses, telangiectasis, and ulcerations.<sup>6,15</sup> Ecchymoses and minor lacerations of the vagina may occur after coitus or during examination, resulting in bleeding or spotting. In premenopausal women, vaginal fluid is clear or white, odorless, and nonirritating. In menopausal woman, as a result of estrogen deprivation, vaginal fluid becomes scanty and yellowish, and lubrication during sexual activity diminishes.<sup>19</sup>

### TABLE: SIGNS OF VAGINAL ATROPHY

- Pale, smooth, or shiny epithelium
- Sparsity of pubic hair
- Dryness of labia, fusion of labia minora
- Introital stenosis
- Changes in the quantity and quality of vaginal secretions
- Vulvar loss of collagen, adipose, and water-retaining ability
- Shortening and narrowing of the vaginal canal
- Changes in the vaginal walls, which become thinner, less elastic, and pale, with loss of rugation
- Changes in the vaginal surface, which becomes friable, with petechiae, ulcerations, and bleeding often occurring after minimal trauma
- Changes in the clitoris: atrophy of the prepuce, loss of its protective covering, greater likelihood of becoming irritated

Adapted from Mehta and Bachmann<sup>21</sup> and Castelo-Branc et al.<sup>22</sup>

Vestibular tenderness may be observed on palpation and may hinder examination. If the introital opening does not appear to allow the width of two fingers, the clinician should consider using a pediatric-size speculum or postponing the examination. A course of estrogen cream applied prior to the next visit may facilitate a more comfortable examination.

**Diagnosis**—Vaginal pH in premenopausal women is naturally low (4.0-5.0) and acts as a barrier to prevent colonization by pathogenic bacteria.<sup>20</sup> The acidic pH is maintained by the presence of lactobacilli that act on glycogen in the exfoliating vaginal cells, converting it to lactic acid.<sup>20</sup> Measurement of vaginal pH is considered a practical and cost-effective approach to diagnosing atrophy. Clinicians can test vaginal pH of the lateral vaginal wall using standard pH paper. If the pH is  $\geq 5.0$ , the clinician can communicate to the patient: “It looks as though the acid–base balance in the vagina differs from the last time I saw you. Have you been experiencing any problems with vaginal discharge or any discomfort associated with sexual activity?”

The vaginal epithelium is composed of stratified squamous cells. In samples obtained from menopausal women, clinicians can typically visualize, using wet-mount microscopy,  $>1$  white blood cell per epithelial cell, immature vaginal epithelial cells with relatively large nuclei (parabasal cells), and reduced lactobacilli.<sup>21,22</sup> Cytomorphometric examination of smears from the upper one-third of the atrophic vagina demonstrates an increased proportion of parabasal cells versus superficial cells.<sup>6,21</sup> A diagnosis of bacterial vaginosis (BV) should be ruled out for a woman with increased vaginal pH. Many women with hypoestrogenic vaginal tissue may experience an increase in BV episodes.

The vaginal maturation index (VMI) is a ratio of parabasal, intermediate, and superficial squamous cells found on the cytologic smear.<sup>21</sup> The number of mature squamous cells in hypoestrogenic patients is low ( $<5$ ) when compared with that in normal, healthy women. In response to local estrogen therapy (ET), the VMI shows an increase in the proportion of superficial cells and a decrease in intermediate and parabasal cells.<sup>23</sup> The VMI can be helpful in the diagnosis of atrophy or as an indicator of a positive response to ET.

**Other Causes of Vulvovaginal Symptoms in Menopausal Women**—During the perimenopausal years, vulvovaginal symptoms may be attributed to infectious, inflammatory, or even psychological causes. Inflammatory conditions of the vulva, such as contact dermatitis, squamous hyperplasia, or lichen sclerosus, can cause severe pruritus, soreness, pain, and dyspareunia.

Use of antidepressants, antihistamines, tamoxifen, or medroxyprogesterone can worsen symptoms of vaginal dryness and irritation.<sup>6</sup> A study determining the effect of smoking on vaginal epithelium concluded that higher incidences of atrophic-type vaginal smears were found in the smoking group, independent of postmenopausal age.<sup>24</sup> This study also demonstrated that smokers had an earlier menopause ( $\sim 2.4$  years sooner) than did nonsmokers. Smoking increases the hepatic metabolism of estrogens,<sup>25</sup> and cessation of smoking may be helpful in alleviating symptoms.

## MANAGEMENT

*The patient's clinician makes a diagnosis of severe vaginal atrophy associated with a loss of estrogen as a consequence of menopause, and discusses several management strategies, including the usefulness and importance of local ET.*

Treatment goals for vaginal atrophy include alleviating symptoms, reversing or

minimizing physiologic changes, and improving quality of life. Care and treatment should be individualized to the patient based on symptoms, health history, and lifestyle.<sup>4</sup> ET is the only therapy that will reverse atrophic changes.

Patient education should focus on basic facts pertaining to sexual health, including anatomic and physiologic changes occurring with age and menopause. Women need to be reassured that these typical symptoms are due to the lack of estrogen. Clinicians can recommend appropriate lifestyle modifications, such as cessation of smoking, regular coital activity, masturbation, and, in those patients with recurrent UTIs, increased intake of fluids (water and cranberry juice) and avoidance of the use of synthetic tight-fitting undergarments, panty liners, or perfumed products that may cause genital irritation.<sup>3</sup> Optimal management of coexisting systemic diseases, such as lupus or diabetes, is highly recommended.<sup>3,4</sup> Regular sexual activity should be encouraged because it helps improve blood flow to pelvic organs and maintain vaginal health.<sup>26</sup>

**Nonhormonal Therapy**—Several over-the-counter vaginal moisturizers and lubricants are considered first-line nonhormonal treatments for vaginal dryness. These products are suitable for women with minimal physiologic changes or symptoms, those who may not be suitable candidates for hormonal treatment, or those who are concerned about hormone use.

Lubricants containing protectants and thickening agents in a water base are considered temporary measures to relieve vaginal dryness and must be applied frequently for continuous relief and reapplied before sexual intercourse. Polycarbophil-based vaginal moisturizers are nonhormonal alternatives to ET that are placed in the vagina up to 3 times weekly to produce a moist film over the vaginal tissue.<sup>27</sup> Hydration of the epithelium lubricates the vaginal wall and reduces the incidence of dyspareunia and vaginal itching and irritation. Moisturizers have been shown to restore vaginal pH and improve cytologic morphology.<sup>27</sup>

Some women taking prescription drugs for menopause-related symptoms also use herbal remedies and/or high-dose vitamins, most often without disclosing the fact to their clinician.<sup>28</sup> Patients should be encouraged to talk to their clinician about such alternative therapies, because these therapies tend to offer little or no relief. In some studies, however, vaginal application of vitamin E oil before coitus has been shown to provide some symptomatic relief,<sup>4,29,30</sup> and vitamin D supplementation has been reported to improve vaginal maturation.<sup>31</sup>

**Local Vaginal Estrogen Therapy**—Local vaginal ET has been demonstrated to be effective in reversing the atrophic changes associated with menopause.<sup>32-34</sup> Recently, 86% of 600 physicians surveyed agreed that local ET was the most effective treatment for postmenopausal vaginal atrophy.<sup>35</sup> Local ET has several advantages over systemic ET, including faster relief of symptoms.<sup>36</sup> Between 80% and 90% of patients experience symptomatic relief within weeks of starting treatment.<sup>4</sup> Significant improvement in vaginal cytologic findings within 14 days of local estrogen administration has been demonstrated.<sup>23,37</sup> Simon and colleagues<sup>23</sup> reported that a significant improvement in VMI started at week 2 and was sustained until week 52. Favorable alterations in the vaginal cellular environment, in combination with increased thickness, make the vaginal epithelium less prone to bleeding and possibly increases vaginal–cervical paracellular permeability, resulting in increased cellular secretions and lubrication.<sup>38</sup>

Current treatment guidelines recommend use of the lowest effective dose of local ET for symptom relief in vaginal atrophy.<sup>39</sup> Lower doses of topical estrogens bypass first-pass metabolism by the liver, thereby limiting systemic exposure and resulting

in fewer side effects.<sup>40</sup> Local ET, compared with systemic ET, has a reduced risk of adverse effects such as breast and endometrial cancers and ischemic heart disease.<sup>29</sup> The dose of estrogen is low enough in all vaginal cream, ring, and tablet formulations so as to not cause excessive endometrial proliferation, obviating the need for the use of progesterone to control proliferation.<sup>4,41</sup> However, prior to treatment, high risk for or history of hormone-dependent cancers must be ruled out.<sup>4</sup>

Several local vaginal ETs are available, including estradiol cream, conjugated estrogen cream, a sustained-release estradiol ring, and a micronized estradiol hemihydrate vaginal tablet.<sup>19</sup> All of these products are effective; however, each formulation has benefits and drawbacks.

**Cream Formulations.** Vaginal creams contain low-dose estrogen. Estrace<sup>®</sup> offers an initial estradiol dosage of 2.0-4.0 g/day for 1-2 weeks, followed by a maintenance dosage of 1.0 g/d; Premarin<sup>®</sup> offers a cyclic dosage of conjugated estrogens 0.5-2.0 g/day; as an alternative, a dosage of 0.5 g twice a week is available.<sup>4</sup> These creams are the most commonly used vaginal ET treatments, especially in women with introital stenosis, which prevents insertion of a vaginal ring or tablet. Creams may be applied directly to the vulva and vulvovaginal area, providing flexibility in dosing and frequency of administration. However, leakage of cream from the vagina is considered an important drawback.<sup>42</sup> Patients must be advised to use the least amount of cream that relieves symptoms.<sup>29</sup>

**Tablet Formulation.** Vagifem<sup>®</sup> tablets contain 25.8 mcg of estradiol hemihydrate, which is equivalent to 25 mcg/day of estradiol (initial dosage, 1 tablet/day for 2 weeks, followed by a maintenance dosage of 1 tablet/twice weekly<sup>4</sup>), in a hydrophilic cellulose-based matrix. Each tablet is steadily absorbed by the atrophic vaginal epithelium; however, absorption is significantly reduced after maturation of the epithelium.<sup>37</sup> Upon contact with the vaginal mucosa, the tablet forms a gel layer, allowing rapid diffusion of estradiol. Studies have shown that the vaginal tablet formulation is more acceptable to patients than are the creams, and that newly treated patients using the vaginal tablet are more likely to continue treatment for longer periods and are more compliant than patients using vaginal creams.<sup>36,43</sup> A reduction in absorption across the vaginal epithelium following epithelial maturation decreases the risk of systemic absorption of estrogen.

**Ring Formulations.** Two vaginal ring formulations are available; both contain sustained-release estradiol and have been shown to be effective in treating symptoms of vaginal atrophy. The rings are inserted once every 90 days, and release a specific amount of estradiol every 24 hours. Estring<sup>®</sup>, a local vaginal ET product, contains 2 mg of estradiol and releases 7.5 mcg/day. Femring<sup>®</sup>, a systemic ET product, contains 12.4 or 24.8 mg of estradiol and releases 0.05-0.10 mg/day,<sup>4</sup> producing systemic levels. A drawback of the vaginal rings is that they are prone to displacement with bowel movements, sexual intercourse, douching, and Valsalva maneuvers.<sup>4</sup>

#### CONTRAINDICATIONS TO ESTROGEN THERAPY

Contraindications to ET include estrogen-sensitive tumors, end-stage liver failure, and past history of estrogen-related thromboembolism. Possible adverse effects of ET include breast tenderness, vaginal bleeding, risk of estrogen-dependent neoplasms, paresthesias, benign endometrial disorders, and increased susceptibility to vaginal candidiasis.<sup>3,4,44</sup> However, no evidence suggests that women on low-dose ET need to undergo routine endometrial screening.<sup>4</sup> Several clinical trials are under way to further investigate the safety and efficacy of ET.

Patient preference is an important criterion, along with lifestyle, in selecting the most appropriate treatment delivery route for each woman. Women considering ET

should be counseled on the benefits and risks of treatment, as well as the advantages and disadvantages of each particular product.

#### EMERGING THERAPIES

Emerging therapies for vaginal atrophy include microdose transdermal ET,<sup>45</sup> intravaginal dihydroepiandrosterone,<sup>46</sup> synthetic conjugated estrogen creams,<sup>47</sup> ultra-low-dose vaginal estradiol tablets,<sup>23</sup> systemic therapy with selective estrogen receptor modulators (SERMS), local therapy with vaginal SERMS, and formed-in-place estrogens and androgens (dehydroepiandrosterone is provided vaginally, which is then converted locally in the vaginal epithelium to estrogens and androgens).<sup>48</sup>

#### TREATMENT AND FOLLOW-UP

*The patient's clinician recommends an estrogen vaginal cream to improve vulvar irritation. After 2 weeks of treatment, the patient calls and reports that she feels better. She has noticed that her underwear is wet and wonders if there is something other than the cream that may be as effective but a little less "messy." The clinician prescribes the vaginal tablet and instructs the patient to insert it as high into the vagina as is comfortable so that the temperature and moisture can aid in absorption. The initial use of the estrogen cream, because of its local effect on the introitus, has facilitated insertion of the vaginal tablet for this patient.*

Because of the lack of long-term clinical trial data, no specific protocol for follow-up is available for long-term use (>12 months) of local vaginal ET.<sup>3,4</sup> A retrospective study conducted on >13,000 women assessed refill-based treatment duration and adherence to low-dose vaginal ET, and showed that duration of local ET in the real-life setting exceeds 12 months.<sup>36</sup>

#### CONCLUSION

Estrogen deprivation in menopause is the main cause of vaginal atrophy, resulting in vaginal dryness, thinning of tissues, and dyspareunia. Despite the availability of several safe and effective therapies, detection of vaginal atrophy is complicated because of patients' hesitancy to report symptoms and inadequate evaluation and treatment by clinicians. Choice of appropriate therapy is based on a patient's symptoms and lifestyle. Local administration of estrogen can reverse signs and symptoms of vaginal atrophy without systemic adverse events. Adequate therapy requires continuous treatment, but no protocol for long-term follow-up of patients on local ET exists right now. Patients should be advised regarding the importance of periodic follow-up, possible side effects, and the need to promptly report symptoms to their clinician.

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